REMARKS

Upon entry of this amendment, claims 34-36 and 38-48 will be canceled without prejudice of disclaimer of the subject matter recited therein and without prejudice to the filing of one or more continuation and/or divisional applications directed to the canceled subject matter. Claims 24, 28, 29, 32, 33 and 37 will be amended. Claims 24, 28, 29, 32, 33 and 37 will remain pending.

The amendment herein is enterable after final rejection as the amendment has been presented to simplify issues for consideration by the Examiner and places the application in better form for appeal or allowance. In particular, the independent claims have been amended to recite (2E,4E,6E,10E)-3,7,11,15-tetramethyl-2,4,6,10,14-hexadecapentaenoic acid as an active ingredient, which was previously recited in dependent claims 36 and 40. Accordingly, the Examiner has previously considered issues as presented in the instant amendment, and it should not require any undue additional search and/or consideration by the Examiner to enter and consider the amendment herein.

Accordingly, entry of the amendment with reconsideration and allowance of the application are respectfully requested.

Statement of Interview

Applicants express appreciation for the courtesies extended by Examiner Kyle Purdy to Applicants' representative Arnold Turk during an October 27, 2010 telephone interview.

During the interview, the rejection of record was discussed. Applicants' representative noted that one of ordinary skill in the art would not have combined the cited art in the manner contended in the rejection. It was pointed out that it would not have been obvious to treat

arteriosclerosis with an acyclic polyprenyl compound absent knowledge that such a compound inhibits KLF5 and/or inhibits vascular remodeling.

Applicants' representative also noted that the rejection asserts that inhibition of vascular remodeling would be obvious because Marx teaches that PPAR activators (i.e., 3,7,11,15-tetramethyl-2,4,6,10,14 hexadecapentanoic acid) are useful for reducing inflammation in transplant associated arteriosclerosis. It was pointed out that this does not mean that Marx discloses inhibition of vascular remodeling, either explicitly or inherently. It was further pointed out that the rejection appears to concede that any reduction in the expression of proinflammatory cytokines from the activation of PPAR yields only "potential" therapeutic benefits in pathological processes such as atherosclerosis and transplantation-associated arteriosclerosis.

The Examiner contended that Marx discloses, at page 704, left column first full paragraph, that given the role of T-lymphocyte inflammatory cytokine production in atherosclerosis and evidence of PPARs as anti-inflammatory mediators, it is hypothesized that human T lymphocytes express PPARα and PPARγ and that stimulation of these cells by PPAR activators in clinical use would limit inflammatory cytokine expression. Moreover, the Examiner contended that Shidoji discloses that acyclic polyprenyl compounds are activators of PPAR. The Examiner contended that in view of such disclosure there is a reasonable expectation of success of using the acyclic polyprenyl compounds of Shidoji with the disclosure of Marx to treat atherosclerosis and Applicants' recited subject matter would be at hand.

Response To Requirement For Restriction

The Office Action includes claims 33-40 with the claims under examination, and holds claims 41-48 as non-elected by original presentation.

In response, Applicants have canceled non-elected claims 41-48 without prejudice to the filing of the non-elected claims in one or more divisional applications.

Response to Rejection under 35 U.S.C. 103(a)

Claims 24, 28, 29, and 32-40 under 35 U.S.C. 103(a) as being unpatentable over Marx et al. (*Circ. Res.* **90**:703-710, 2002; hereinafter "Marx") in view of Shidoji et al. (WO 01/80854; hereinafter "Shidoji") as evidenced by the English equivalent US2005/0250671.

In response, Applicants submit for the arguments already of record, the claims presented herein as well as prior to the present amendment are patentable over the prior art of record. However, in an attempt to advance prosecution of the application, Applicants have amended the independent claims, as noted above, to recite (2E,4E,6E,10E)-3,7,11,15-tetramethyl-2,4,6,10,14-hexadecapentaenoic acid as an active ingredient.

Thus, for the reasons set forth in Applicants' Amendment Under 37 C.F.R. 1.111, filed June 29, 2010, which are incorporated by reference herein as if set forth in their entirety, and for the reasons set forth below, Applicants' claimed subject matter is patentable over the prior art of record and the rejections of record should be withdrawn as a *prima facie* case of obviousness has not been established.

Moreover, even if for the sake of argument a *prima facie* case of obviousness has been established, Applicants' claimed subject matter provides unexpected advantages. As will be shown below, (2E,4E,6E,10E)-3,7,11,15-tetramethyl-2,4,6,10,14-hexadecapentaenoic acid (NIK-333)" as recited in Applicants' claims provides advantageous effects as shown with respect to ATRA (all-trans retinoic acid) in view of the experimental results in Example 5 of Applicants' specification for KLF5 inhibition and Example 3-2 for vascular remodeling.

As can be understood from the experimental results of Example 5, at page 11 of Applicants' specification and as illustrated in Fig. 5, NIK-333 provides more potent inhibitory action than ATRA (which was used as a comparative retinoid) against the proliferation of the tested 3T3-KLF5 cells in which KLF5 were stably expressed. In this regard, KLF5 has the action of stimulating proliferation of cells (see, for example, Miyamoto et al., Molecular and Cellular Biology, Vol. 23, No. 23, Dec. 2003, pp. 8528-8541, such as in the abstract thereof, at lines 4 and 5). In contrast, prior to Applicants' invention, it was known in the field of art that the pharmacological action of ATRA via the retinoid receptor is more potent than NIK-333 (see, Tsurumi et al., International Journal of Hematology, 59, pp. 9-15, 1993 wherein E5166 corresponds to NIK-333).[1] Therefore, the experimental results of Example 5 in Applicants' specification as originally filed establish unexpected results of Applicants' recited (2E,4E,6E,10E)-3,7,11,15-tetramethyl-2,4,6,10,14-hexadecapentaenoic acid. Accordingly, one having ordinary skill in the art would not have expected the results as illustrated in Applicants' originally filed application.

Further, the action of NIK-333 against vascular remodeling was revealed to be more potent than ATRA in Example 3-2 of Applicants' specification by using the mouse cuff-induced injury model, as see pages 9 and 10, and Table 2 of Applicants' specification. Accordingly, one of ordinary skill in the art would not have been able to expect the superior action of NIK-333 than ATRA.

Applicants therefore respectfully request reconsideration of the obviousness rejection and withdrawal of the same.

[1] These documents are being submitted in accordance with MPEP 609(C)(3) as part of Applicants' reply to the Office Action in support of an argument so that the requirements of 37 C.F.R. 1.97 and 1.98 need not be met, and the information is being submitted as part of the record with the reply for the Examiner's consideration with Applicants' reply.

CONCLUSION

For the reasons discussed above, it is respectfully submitted that the rejections be withdrawn.

Favorable consideration with early allowance of all of the pending claims is most earnestly requested.

If there are any questions regarding the application in general, or the remarks set forth herein, a telephone call to the undersigned would be appreciated since this should expedite the prosecution of the application.

Respectfully Submitted,
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